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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 15

Application Number: 10/006,163
Filing Date: December 04, 2001
Appellant(s): LAL ET AL.

Terence P. Lo
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 7/2/03

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellant's Bief includes statements that

As to issue 1, claims 11, 36 and 37 are group together,

As to issue 2, claims 11, 31, 42 and 43 are group together,

As to Issue 3, claims 11 and 31 are grouped together,

As to issue 4, Claims 11, 31, 32 and 34 are group together,

As to issue 5, claims 11 and 38-41 are group together,

As to issue 6, all of the claims on appeal are grouped together,

As to issue 7, all of the claims on appeal are grouped together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

6,180,370	Queen	01-2001
4,946,778	Ladner	8-1990

Verwoert, I. "Cloning, Nucleotide Sequence, and Expression of the Escherichia coli fabD Gene, Encoding Malonyl Coenzyme A-Acyl Carrier Protein Transacylase" J Biol Chem, Vol 174, no. 9 (May 1992), pp. 2851-2857.

Harlow, E. in Antibodies a Laboratory Manual, 1988, Cold Spring Harbor Laboratory Publication, Cold Spring Harbor, NY, pp. 93, 139-149, 319-356, and 626-629.

Abaza, M. "Effects of Amino Acid Substitutions Outside an Antigenic Site on Protein Binding to Monoclonal Antibodies of Predetermined Specificity Obtained by Peptide Immunization: Demonstration with Region 94-100 (Antigenic Site 3) of Myoglobin" J. of Protein Chemistry, vol 11, no. 5 (1992), pp. 433-444.

Kuby, J. in Immunology, second edition, (1994), pp. 85-96.

Ngo, J.T. "Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" in The Protein Folding Problem and Tertiary Structure Prediction (1994), pp.491-495.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

Claims 11 and 36-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Verwoert *et al* (J Bioteriol 174: 2851-57, 1992; PTO 892).

Verwoert *et al* teach an antibody that specifically binds to an epitope, which is a fragment such as VTGASRGIGRGIA of a polypeptide such as Malonyl coenzyme A-Acyl carrier protein transacylase that has a stretch of contiguous amino acid residues (epitope) identical to the claimed SEQ ID NO: 1 (See Fig 2, last full line, Fig 3, page 2853, in particular). The reference antibody binds specifically to a fragment such as VTGASRGIGRGIA (13 amino acids), which is an epitope of the fragment of at least 15 contiguous amino acid residues of SEQ ID NO: 1. Verwoert *et al* further teach a method of preparing a polyclonal antibody comprising immunizing an animal such as a mouse with the reference immunogenic fragment to elicit antibody response, isolating antibodies from said animal where the reference antibody would cross-react with the claimed SEQ ID NO: 1 (See Production of Antibodies and Immunodetection, in particular). While the reference is silent that the reference antibody binds to SEQ ID NO: 1, the reference antibody has the same binding specificity of claimed antibody since the reference antibody binds specifically to a fragment such as VTGASRGIGRGIA (13 amino acids), which is an epitope of the fragment of at least 15 contiguous amino acid residues of SEQ ID NO: 1. Therefore the claimed antibody appears to be the same as the prior art antibody. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

1. Claims 11, 31, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verwoert *et al* (J Bioteriol 174: 2851-57, 1992; PTO 892) in view of US Pat No. 6,180,370B, filed June 1995; PTO 892).

The teachings of Verwoert *et al* have been discussed supra. Verwoert *et al* further teach the reference polypeptide is a temperature labile malony CoA ACP transacylase that plays a role in transferring the malonyl and/or acetyl group in the biosynthesis of polypeptides (See page 2855, Discussion, in particular). Verwoert *et al* teach the reference antibody is useful for immunodetection (See page 2853, column 1, in particular).

The claimed invention in claim 31 differs from the teachings of the reference only that the antibody is a chimeric antibody, or a humanized antibody.

The claimed invention in claim 42 differs from the teachings of the reference only that the antibody is produced by screening a Fab expression library.

The claimed invention in claim 43 differs from the teachings of the reference only that antibody is produced by screening a recombinant immunoglobulin library.

The '370 patent teaches a method of producing chimeric antibodies (See column 55 lines 25-59; column 59, lines 65, in particular) and humanized antibodies (See column 44 line 33; column 68 lines 8-44, in particular) by screening a Fab expression library or a recombinant immunoglobulin library. The reference chimeric antibody comprises a variable region of an antibody and a human immunoglobulin constant region. The '370 patent further teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce chimeric antibody or humanized antibody by screening Fab expression library or recombinant immunoglobulin antibody as taught by the '370 patent that binds specifically to an epitope such as VTGASRGIGRGIA as taught by Verwoert *et al* that is identical to an epitope in the claimed SEQ ID NO: 1. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '370 patent teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular). Verwoert *et al* teach the reference antibody to the reference polypeptide is useful for immunodetection (See page 2853, column 1, Discussion, in particular).

2. Claims 11 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verwoert *et al* (J Bioteriol 174: 2851-57, 1992; PTO 892) in view of US Pat No. 4,946,778 (Aug 1990, PTO 892).

The teachings of Verwoert *et al* have been discussed supra.

The claimed invention in claim 31 differs from the teachings of the reference only that the antibody is a single chain antibody.

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody or a polypeptide fragment (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to make single chain antibody as taught by the '778 patent that binds specifically to epitope such as VTGASRGIGRGIA as taught by Verwoert *et al* that is identical to an epitope in the claimed SEQ ID NO: 1. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

3. Claims 11, 31-32, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verwoert *et al* (J Bioteriol 174: 2851-57, 1992; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 319-356, and 626-629).

The teachings of Verwoert *et al* have been discussed supra.

The claimed invention as recited in claim 31differs from the teachings of the reference only by the recitation that the antibody is a Fab fragment, a F(ab')2 fragment.

The claimed invention as recited in claim 32 differs from the teachings of the reference only by the recitation of a composition comprising said antibody and an acceptable excipient.

The claimed invention as recited in claim 34 differs from the teachings of the reference only that the antibody is labeled.

Harlow *et al* teach a method of producing antibody fragment wherein the fragment is Fab or F(ab')2 fragment (See page 626-629, in particular). Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). Harlow *et al* further teach labeling any antibody with various labels such as enzyme or FITC (See chapter 9, in particular) in a composition comprising an antibody and a carrier such as PBS (See page 354, in particular) or NaCl, which is a saline solution (See page 346, in particular) for various detection assays. The advantages of enzyme labeling are longer shelf life, and higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce antibody fragment such as Fab or F(ab')2 or to label any antibody as taught by Harlow *et al* with the polyclonal antibody that binds specific to a epitope or fragment comprises a contiguous amino acid residues VTGASRGIGRGIA which is identical to an epitope in the claimed SEQ ID NO: 1 as taught by Verwoert *et al* and Harlow *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach antibody fragments can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular) and the labeled antibody can be used for various detection assays. The advantages of enzyme labeling

are longer shelf life, higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

4. Claims 11 and 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verwoert *et al* (J Bioteriol 174: 2851-57, 1992; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-149).

The teachings of Verwoert *et al* have been discussed supra.

The claimed invention as recited in claim 38 differs from the teachings of the reference only that a composition comprising the polyclonal antibody and a suitable carrier.

The claimed invention as recited in claim 39 differs from the teachings of the reference only that a method of making monoclonal antibody comprising immunizing an immunogenic fragment thereof.

The claimed invention as recited in claim 40 differs from the teachings of the reference only that a composition comprising the monoclonal antibody produced by the method of claim 39.

The claimed invention as recited in claim 41 differs from the teachings of the reference only that a composition comprising the monoclonal antibody and a suitable carrier.

Harlow *et al* teach a method of producing polyclonal antibody using rabbit for practical reasons because they are easy to keep and handle and antibody produced are well characterized and easily purified (See page 93, in particular). Harlow *et al* further teach a method of producing monoclonal antibody (See page 139-149, in particular) and the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular). Harlow *et al* further teach labeling any antibody with various label such as enzyme or FITC (See chapter 9, in particular) in a composition comprising an antibody and a carrier such as PBS (See page 354 in particular) or NaCl, which is a saline solution (See page 346) for various detection assays. The advantages of enzyme labeling are longer shelf life, higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody as taught by Harlow *et al* with the

polypeptide as taught by Verwoert *et al* for a composition comprising said antibody and a carrier such as PBS as taught by Harlow *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make monoclonal antibody that binds to any immunogenic fragment because Harlow *et al* teach that the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular).

Claim Rejections - 35 USC § 112 First Enablement

Claims 11, 31-32, 34, 36-43 and 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or an immunogenic fragment thereof wherein the fragment has CoA dehydrogenase activity, (2) a composition comprising said antibody and an acceptable excipient for competitive binding or immunoradiometric assays or for detection assays, (3) the said composition wherein the antibody is labeled, (4) a method of preparing a polyclonal, or a monoclonal antibody with the specificity of the antibody that binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, (5) a polyclonal or a monoclonal antibody produced by said method, (6) a composition comprising said polyclonal or monoclonal antibody, and a suitable carrier, and (7) the said antibody wherein the antibody is produced by screening a Fab expression library, or recombinant immunoglobulin library, **does not** reasonably provide enablement for (1) *any* isolated antibody as set forth in claims 11, 31-32, 34, 36-43 and 58 for treating any immune disorder such as cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable

one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only antibody that specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, a composition comprising said antibody or a labeled antibody that binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 for diagnostic and detection assays. The specification on page 14 discloses the term "variant" of human short chain dehydrogenase (HSCD) is any amino acid sequence that is altered by one or more amino acids such as substitution, insertion and deletion (See page 14 of specification, second full paragraph). The specification on page 8 defines the term "epitope" is a fragment of a molecule that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinant (epitope) given regions or three dimensional structures on the protein. The epitope may compete with intact antigen for binding to an antibody. The specification on page 7 line 7 defines the term "immunogenic fragment" is any fragment of HSCD which are preferably about 5 to about 15 amino acids in length which retain some biological activity or immunological activity of HSCD.

The specification does not teach how to make any antibody mentioned above that binds to any polypeptide "comprising" any fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO: 1 because the term "comprising" is open-ended. It expands the polypeptide fragment to which the antibody binds to include additional amino acid residues at either or both ends. There is insufficient guidance as to the binding specificity of the claimed antibody and the immunogen used by applicant to generate antibody that would bind specifically not only to SEQ ID NO: 1, but also to a polypeptide having undisclosed amino acids at either or both ends.

With regard to antibody that binds to any epitope of any polypeptide having only 90% identity to SEQ ID NO: 1, a 90% identity is 10% difference in SEQ ID NO: 1, which is equivalent to having 31 amino acids difference (SEQ ID NO 1 which has 313 amino acids and multiply that by 10%) in any region of SEQ ID NO: 1. The specification does not provide guidance as to which one or more amino acids of SEQ ID NO: 1 is altered such as substitution, insertion and deletion and whether the resulting polypeptide variant has any biological function. There is no working example in specification as filed of any variants of SEQ ID NO: 1. Further,

there is insufficient guidance as to the binding specificity of the claimed antibody since the epitope to which the antibody binds is not disclosed.

Abaza *et al,* of record, teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity (binding) of a protein with monoclonal antibody against the site (See abstract, in particular).

Kuby *et al,* of record, teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues (fragment) or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide, let alone a polypeptide with 10% difference compared to SEQ ID NO: 1 or any polypeptide having undisclosed amino acid at either or both ends. In the absence of guidance as to the specific amino acid residues (the antigenic determinant) used by applicant for immunization and the specific epitope of SEQ ID NO: 1, or fragment thereof to which the antibody binds, it is unpredictable which antibody generated from the full length polypeptide of SEQ ID NO: 1 would bind specifically to an undisclosed polypeptide having addition, deletion, and insertion or fragment of SEQ ID NO: 1. Even if the fragment is limited to consisting of 15 contiguous amino acid residues of SEQ ID NO: 1, the antibody generated from said fragment may not bind to the full-length polypeptide of SEQ ID NO: 1 as taught by Kuby et al, let alone variant of SEQ ID NO: 1 that has 10% difference.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Given the lack of guidance as to which amino acid within the polypeptide of SEQ ID NO: 1 can be substitute, delete, or add and retain function, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention. Since the variant of SEQ ID NO: 1 such as any polypeptide that is 90% identical to SEQ ID NO: 1 is not enabled, it follows that the method of making antibody that binds to any undisclosed variant of SEQ ID NO: 1 is not enabled.

With regard to antibody which binds to a polypeptide "comprising" any "fragment" of a polypeptide, such as any fragment "comprises" at least 15 contiguous amino acid residues of SEQ ID NO: 1 and wherein the antibody specifically binds to an epitope of the fragment, the term "comprising" is open-ended. It expands the fragment to include additional amino acid residues at either or both ends. There is insufficient guidance as to the structure of the fragment to which the

antibody binds, much less which epitope within the fragment having additional undisclosed amino acid residues at either or both ends. Further, there are no working examples demonstrating any antibody can bind to any fragment and variants of SEQ ID NO: 1. Since the binding specificity of the antibody is not enable, it follows that the composition comprising any antibody such as chimeric, single chain, Fab fragment, F(ab')2 fragment, humanized antibody monoclonal, polyclonal is not enabled. It also follows that any labeled antibody mentioned above is not enabled. It also follows that the method of making any polyclonal and monoclonal antibody is not enabled because the specific amino acid sequence of the immunogen to make said antibody is not disclosed. It also follows that any antibody produced by a Fab expression library or by screening a recombinant immunoglobulin library is not enabled because the fragment "comprises" the undisclosed amino acid residues at either or both ends.

The '370 patent teaches that the inherent problem with chimeric antibody has been a loss of affinity for the antigen, which means more antibody will have to be injected into a patient at higher cost and greater risk of adverse effects such as serum sickness (See column 2 lines 12-27, in particular). In the absence of in vivo working examples, it is unpredictable for the following reasons: (1) the antibody may be inactivated before producing an effect, i.e. such as inherently short half-life of the antibody; (2) the antibody may not reach the target area; and (3) other functional properties, known or unknown, may make the antibody unsuitable for *in vivo* therapeutic use, i.e. such as serum sickness which prohibitive to the use of antibody for such treatment. Therefore, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Claim Rejections - 35 USC § 112 First Written Description

Claims 11, 31-32, 34, 36-43 and 58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* isolated antibody such as chimeric, single chain, Fab fragment, F(ab')2 fragment, humanized antibody monoclonal, polyclonal which specifically binds to *any* epitope of a polypeptide at least 90% identical to SEQ ID NO: 1, and any isolated antibody that binds to *any* epitope of *any* immunogenic fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO: 1 for detection assays.

The specification discloses only antibody that specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, a composition comprising said antibody or a labeled antibody that binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 for diagnostic and detection assays. The specification on page 14 discloses the term "variant" of human short chain dehydrogenase (HSCD) is any amino acid sequence that is altered by one or more amino acids such as substitution, insertion and deletion (See page 14 of specification, second full paragraph). The specification on page 8 defines the term "epitope" is a fragment of a molecule that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinant (epitope) given regions or three dimensional structures on the protein. The epitope may compete with intact antigen for binding to an antibody. The specification on page 7 line 7 defines the term "immunogenic fragment" is any fragment of HSCD which are preferably about 5 to about 15 amino acids in length which retain some biological activity or immunological activity of HSCD.

With the exception of the specific antibody that binds to the specific polypeptide of SEQ ID NO: 1 mentioned above, there is insufficient written description about the structure of *any* immunogenic fragment "comprises" at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO: 1 because the term "comprising" is open-ended. It expands the fragment to include additional amino acids at either or both ends. There is inadequate written description about the

undisclosed amino acids at either or both ends of the fragment, much less about the epitope to which the antibody binds in said undisclosed fragment.

Further, there is insufficient written description about the structure such as the specific amino acid sequence of any polypeptide that is at least 90% identical to SEQ ID NO: 1 to which the antibody binds. A 90% identity to SEQ ID NO: 1 means 10% difference, which is equivalent to having 31 amino acids difference (SEQ ID NO 1 which has 313 amino acids and multiply that by 10%) in any region of SEQ ID NO: 1. Given the indefinite number of undisclosed polypeptide that is at least 90% identical to SEQ ID NO: 1, the variants of SEQ ID NO: 1 is not adequately described. Since the variants of SEQ ID NO: 1 is not adequately described, it follows that the claimed antibody that binds to any variants of SEQ ID NO: 1 such as any polypeptide that is at least 90% identical to SEQ ID NO: 1 is not adequately described.

Finally, In the absence of guidance as to the specific amino acid residues (the epitope) to which the claimed antibody binds or makes contact (the binding specificity), the claimed antibody could bind to the non disclosed amino acids (the 10%) of a variant of SEQ ID NO: 1, that is still 90% identical to SEQ ID NO: 1. Given the lack of a written description of any additional variants of SEQ ID NO: 1 or immunogenic fragment of SEQ ID NO: 1 to which the claimed antibody that binds, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

(11) Response to Argument

Issue 1 -Whether Claims 11, 36 and 37 are anticipated under 35 USC §102(b) by Verwoert et al.

At page 5 of the Brief, Appellants argue that the while it may be true that the antibodies taught by Verwoert et al could possibly bind to a polypeptide comprising SEQ ID NO: 1 or fragments or variants thereof, this binding would not be specific. The antibodies recited by the claims specifically bind to a polypeptide comprising SEQ ID NO: 1 or fragments or variants thereof. The antibodies taught by Verwoert et al are excluded from the claimed antibodies because they bind to polypeptides other than those recited in the claims.

Appellants' arguments have been fully considered but are not found to be persuasive. The amended claim 11 filed concurrently herewith still encompasses any antibody that binds to any epitope of SEQ ID NO: 1, any epitope of a polypeptide at least 90% identical to SEQ ID NO: 1 and any polypeptide "comprising" an immunogenic fragment of SEQ ID NO: 1 wherein said fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO: 1 and wherein the antibody binds to any epitope of the fragment.

Verwoert *et al* teach an antibody that specifically binds to an epitope, which is a fragment such as VTGASRGIGRGIA of a polypeptide such as Malonyl coenzyme A-Acyl carrier protein transacylase that has a stretch of contiguous amino acid residues (epitope) *identical* to the claimed SEQ ID NO: 1 (See Fig 2, last full line, Fig 3, page 2853, in particular). The reference antibody binds specifically to a fragment such as VTGASRGIGRGIA (13 amino acids), which is an epitope of the fragment of at least 15 contiguous amino acid residues of SEQ ID NO: 1. Verwoert *et al* teach a method of preparing a polyclonal antibody comprising immunizing an animal such as a mouse with the reference immunogenic fragment to elicit antibody response, isolating antibodies from said animal where the reference antibody would cross-react with the claimed SEQ ID NO: 1 because of the reference antibody binds to the same epitope VTGASRGIGRGIA (13 amino acids) of at least 15 contiguous amino acid residues of the claimed SEQ ID NO: 1 (See Production of Antibodies and Immunodetection, in particular). In other words, the reference antibody would also cross-react with the variants and fragments of SEQ ID NO: 1. In fact, Appellants state on record that the reference antibodies taught by Verwoert et al could possibly bind to a polypeptide comprising SEQ ID NO: 1 or fragments or variants thereof, this binding would not be specific. However, in the absence of specific teachings that specific binding is not equate with cross-reactivity, the claimed antibody appears to be the same as that of the reference antibody. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

Issue 2 - Whether Claims 11, 31, 42 and 43 are obvious under 35 USC §103(a) over Verwoert et al in view of US Pat No 6,180,370.

At page 6 of the Brief, Appellants argue that the antibodies recited by the claims specifically bind to a polypeptide comprising SEQ ID NO: 1 or fragments or variants thereof. The antibodies taught by Verwoert et al are excluded from the claimed antibodies because they bind to polypeptides other than those recited in the claims. Since the claim language distinguishes the recited antibodies from the antibodies taught by Verwoert et al, the Examiner has not convincingly show how the teachings of the Verwoert et al and/or Queen et al could be modified in order to arrive at the claimed subject matter. Claim 11 has been amended by the amendment filed concurrently herewith.

Appellants' arguments have been fully considered but are not found to be persuasive. Although claim 11 has been amended, the amended claim 11 filed concurrently herewith still encompasses any antibody that binds to any epitope of SEQ ID NO: 1, any epitope of a polypeptide at least 90% identical to SEQ ID NO: 1 and any polypeptide "comprising" an immunogenic fragment of SEQ ID NO: 1 wherein said fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO: 1 and wherein the antibody binds to any epitope of the fragment.

In response to Appellants' argument that the antibody taught by Verwoert et al are excluded from the claimed antibodies, the claimed antibodies would include the antibody of Verwoert et al because the antibodies would cross-react with the variants and fragments of the claimed polypeptide of SEQ ID NO: 1. In fact, Appellants state on record that the reference antibody taught by Verwoert et al could possibly bind to epitope on a polypeptide comprising SEQ ID NO: 1 or fragments or variants thereof, this binding would not be specific. However, in the absence of specific teachings that specific binding is not equate with cross-reactivity, the claimed antibodies appear to be the same as that of the reference antibody since the claimed antibodies would bind to the same epitope as the antibody taught by Verwoert et al. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

In response to Appellants' argument that the teachings of the Verwoert et al and/or Queen et al could be modified in order to arrive at the claimed subject matter, Verwoert *et al* teach an

antibody that specifically binds to an epitope, which is a fragment such as VTGASRGIGRGIA of a polypeptide such as Malonyl coenzyme A-Acyl carrier protein transacylase that has a stretch of contiguous amino acid residues (epitope) *identical* to the claimed SEQ ID NO: 1 (See Fig 2, last full line, Fig 3, page 2853, in particular). The reference antibody binds specifically to a fragment such as VTGASRGIGRGIA (13 amino acids), which is an epitope of the fragment of at least 15 contiguous amino acid residues of SEQ ID NO: 1. Verwoert *et al* further teach the reference antibody is useful for immunodetection (See page 2853, column 1, in particular).

The claimed invention in claim 31 differs from the teachings of the reference that the antibody is a chimeric antibody, or a humanized antibody.

The claimed invention in claim 42 differs from the teachings of the reference only that the antibody is produced by screening a Fab expression library.

The claimed invention in claim 43 differs from the teachings of the reference only that the antibody is produced by screening a recombinant immunoglobulin library.

The '370 patent teaches a method of producing chimeric antibodies (See column 55 lines 25-59; column 59, lines 65, in particular) and humanized antibodies (See column 44 line 33; column 68 lines 8-44, in particular) by screening a Fab expression library or a recombinant immunoglobulin library. The reference chimeric antibody comprises a variable region of an antibody and a human immunoglobulin constant region. The '370 patent further teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce chimeric antibody or humanized antibody by screening Fab expression library or recombinant immunoglobulin antibody as taught by the '370 patent that binds specifically to an epitope such as VTGASRGIGRGIA as taught by Verwoert *et al* that is identical to the epitope of the claimed SEQ ID NO: 1. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '370 patent teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen

and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular). Verwoert *et al* teach that antibody to the reference polypeptide is useful for immunodetection (See page 2853, column 1, Discussion, in particular).

Issue 3 - Whether Claims 11 and 31 are obvious under 35 USC §103(a) over Verwoert et al in view of US Pat No 4,946,778.

At page 7 of the brief, Appellants argue that the claims recite antibodies which specifically bind to a polypeptide of SEQ ID NO: 1 or fragments or variants thereof. The antibodies taught by Verwoert et al are excluded from the claimed antibodies because they bind to polypeptides other than those recited in the claims. Since the claim language distinguishes the recited antibodies from the antibodies taught by Verwoert et al, the Examiner has not convincingly show how the teachings of the Verwoert et al and/or Ladner et al could be modified in order to arrive at the claimed subject matter. Claim 11 has been amended by the amendment filed concurrently herewith.

Appellants' arguments have been fully considered but are not found to be persuasive. Although claim 11 has been amended, the amended claim 11 filed concurrently herewith still encompasses any antibody that binds to any epitope of SEQ ID NO: 1, any epitope of a polypeptide at least 90% identical to SEQ ID NO: 1 and any polypeptide "comprising" an immunogenic fragment of SEQ ID NO: 1 wherein said fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO: 1 and wherein the antibody binds to any epitope of the fragment.

In response to Appellants' argument that the antibody taught by Verwoert et al are excluded from the claimed antibodies, the claimed antibodies would include the antibody of Verwoert et al because the antibodies would cross-react with the variants and fragments of the claimed polypeptide of SEQ ID NO: 1. In fact, Appellants state on record that the reference antibody taught by Verwoert et al could possibly bind to epitope on a polypeptide comprising SEQ ID NO: 1 or fragments or variants thereof, this binding would not be specific. However, in the absence of specific teachings that specific binding is not equate with cross-reactivity, the claimed antibodies appear to be the same as that of the reference antibody since the claimed antibodies would bind to the same epitope as the antibody taught by Verwoert et al. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the

instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

In response to Appellants' argument that the teachings of the Verwoert et al and/or Ladner et al could be modified in order to arrive at the claimed subject matter, the teachings of Verwoert *et al* have been discussed supra.

The claimed invention in claim 31 differs from the teachings of the reference only that the antibody is a single chain antibody.

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody or a polypeptide fragment (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to make single chain antibody as taught by the '778 patent that binds specifically to epitope such as VTGASRGIGRGIA as taught by Verwoert *et al* that is identical to the epitope of the claimed SEQ ID NO: 1. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular). Verwoert *et al* teach that antibody to VTGASRGIGRGIA is useful for immunodetection (See page 2853, column 1, in particular).

Issue 4 - Whether Claims 11, 31, 32 and 34 are obvious under 35 USC §103(a) over Verwoert et al in view of Harlow et al.

At paragraph bridging page 7-8 of the Brief, Appellants argue that the claims recite antibodies which specifically bind to a polypeptide of SEQ ID NO: 1 or fragments or variants

thereof. The antibodies taught by Verwoert et al are excluded from the claimed antibodies because they bind to polypeptides other than those recited in the claims. Since the claim language distinguishes the recited antibodies from the antibodies taught by Verwoert et al, the Examiner has not convincingly show how the teachings of the Verwoert et al and/or Harlow et al could be modified in order to arrive at the claimed subject matter. Claim 11 has been amended by the amendment filed concurrently herewith. This is not found persuasive for the following reasons.

Appellants' arguments have been fully considered but are not found to be persuasive. Although claim 11 has been amended, the amended claim 11 filed concurrently herewith still encompasses any antibody that binds to any epitope of SEQ ID NO: 1, any epitope of a polypeptide at least 90% identical to SEQ ID NO: 1 and any polypeptide "comprising" an immunogenic fragment of SEQ ID NO: 1 wherein said fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO: 1 and wherein the antibody binds to any epitope of the fragment.

In response to Appellants' argument that the antibody taught by Verwoert et al are excluded from the claimed antibodies, the claimed antibodies would include the antibody of Verwoert et al because the antibodies would cross-react with the variants and fragments of the claimed polypeptide of SEQ ID NO: 1. In fact, Appellants state on record that the reference antibody taught by Verwoert et al could possibly bind to epitope on a polypeptide comprising SEQ ID NO: 1 or fragments or variants thereof, this binding would not be specific. However, in the absence of specific teachings that specific binding is not equate with cross-reactivity, the claimed antibodies appear to be the same as that of the reference antibody since the claimed antibodies would bind to the same epitope as the antibody taught by Verwoert et al. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

In response to Appellants' argument that the teachings of the Verwoert et al and/or Harlow et al could be modified in order to arrive at the claimed subject matter, Verwoert *et al* teach an antibody that specifically binds to an epitope, which is a fragment such as VTGASRGIGRGIA of a polypeptide such as Malonyl coenzyme A-Acyl carrier protein transacylase that has a stretch of contiguous amino acid residues (epitope) *identical* to the claimed

SEQ ID NO: 1 (See Fig 2, last full line, Fig 3, page 2853, in particular). The reference antibody binds specifically to a fragment such as VTGASRGIGRGIA (13 amino acids), which is an epitope of the fragment of at least 15 contiguous amino acid residues of SEQ ID NO: 1. Verwoert *et al* further teach the reference antibody is useful for immunodetection (See page 2853, column 1, in particular).

The claimed invention as recited in claim 31differs from the teachings of the reference only that the antibody is a Fab fragment, a F(ab')2 fragment.

The claimed invention as recited in claim 32 differs from the teachings of the reference only by the recitation of a composition comprising said antibody and an acceptable excipient.

The claimed invention as recited in claim 34 differs from the teachings of the reference only that the antibody is labeled.

Harlow *et al* teach a method of producing antibody fragment wherein the fragment is Fab or F(ab')2 fragment (See page 626-629, in particular). Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). Harlow *et al* further teach labeling any antibody with various labels such as enzyme or FITC (See chapter 9, in particular) in a composition comprising an antibody and a carrier such as PBS (See page 354, in particular) or NaCl, which is a saline solution (See page 346, in particular) for various detection assays. The advantages of enzyme labeling are longer shelf life, and higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce antibody fragment such as Fab or F(ab')2 or to label any antibody as taught by Harlow *et al* with the polyclonal antibody that binds specific to a fragment comprises a contiguous amino acid residues of the claimed SEQ ID NO: 1 as taught by Verwoert *et al* or Harlow *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach antibody fragments can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular) and the labeled antibody can be used for various detection assays. The advantages of enzyme labeling

are longer shelf life, higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Issue 5 - Whether Claims 11 and 38-41 are obvious under 35 USC §103(a) over Verwoert et al in view of Harlow et al (page 139-149).

At paragraph bridging page 8-9 of the Brief, Appellants argue that the claims recite antibodies which specifically bind to a polypeptide of SEQ ID NO: 1 or fragments or variants thereof. The antibodies taught by Verwoert et al are excluded from the claimed antibodies because they bind to polypeptides other than those recited in the claims. Since the claim language distinguishes the recited antibodies from the antibodies taught by Verwoert et al, the Examiner has not convincingly show how the teachings of the Verwoert et al and/or Harlow et al could be modified in order to arrive at the claimed subject matter. Claim 11 has been amended by the amendment filed concurrently herewith. This is not found persuasive for the following reasons.

Appellants' arguments have been fully considered but are not found to be persuasive. Although claim 11 has been amended, the amended claim 11 filed concurrently herewith still encompasses any antibody that binds to any epitope of SEQ ID NO: 1, any epitope of a polypeptide at least 90% identical to SEQ ID NO: 1 and any polypeptide "comprising" an immunogenic fragment of SEQ ID NO: 1 wherein said fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO: 1 and wherein the antibody binds to any epitope of the fragment.

In response to Appellants' argument that the antibody taught by Verwoert et al are excluded from the claimed antibodies, the claimed antibodies would include the antibody of Verwoert et al because the antibodies would cross-react with the variants and fragments of the claimed polypeptide of SEQ ID NO: 1. In fact, Appellants state on record that the reference antibody taught by Verwoert et al could possibly bind to epitope on a polypeptide comprising SEQ ID NO: 1 or fragments or variants thereof, this binding would not be specific. However, in the absence of specific teachings that specific binding is not equate with cross-reactivity, the claimed antibodies appear to be the same as that of the reference antibody since the claimed antibodies would bind to the same epitope as the antibody taught by Verwoert et al. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art

antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

In response to Appellants' argument that the teachings of the Verwoert et al and/or Harlow et al could be modified in order to arrive at the claimed subject matter, Verwoert *et al* teach an antibody that specifically binds to an epitope, which is a fragment such as VTGASRGIGRGIA of a polypeptide such as Malonyl coenzyme A-Acyl carrier protein transacylase that has a stretch of contiguous amino acid residues (epitope) *identical* to the claimed SEQ ID NO: 1 (See Fig 2, last full line, Fig 3, page 2853, in particular). The reference antibody binds specifically to a fragment such as VTGASRGIGRGIA (13 amino acids), which is an epitope of the fragment of at least 15 contiguous amino acid residues of SEQ ID NO: 1. Verwoert *et al* further teach the reference antibody is useful for immunodetection (See page 2853, column 1, in particular).

The claimed invention as recited in claim 38 differs from the teachings of the reference only that a composition comprising the polyclonal antibody and a suitable carrier.

The claimed invention as recited in claim 39 differs from the teachings of the reference only that a method of making monoclonal antibody comprising immunizing an immunogenic fragment thereof.

The claimed invention as recited in claim 40 differs from the teachings of the reference only that a composition comprising the monoclonal antibody produced by the method of claim 39.

The claimed invention as recited in claim 41 differs from the teachings of the reference only that a composition comprising the monoclonal antibody and a suitable carrier.

Harlow *et al* teach a method of producing polyclonal antibody using rabbit for practical reasons because they are easy to keep and handle and antibody produced are well characterized and easily purified (See page 93, in particular). Harlow *et al* further teach a method of producing monoclonal antibody (See page 139-149, in particular) and the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular). Harlow *et al* further teach labeling any antibody with various labels such as enzyme or FITC (See chapter 9, in particular) in a composition comprising an antibody and a carrier such as PBS (See page 354 in particular) or NaCl, which is a saline solution (See page 346) for various detection assays. The advantages of enzyme labeling are longer shelf life, higher sensitivity while the advantages of fluorochrome

label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody as taught by Harlow *et al* that binds specifically to epitope such as VTGASRGIGRGIA as taught by Verwoert *et al* that is identical to the epitope of the claimed SEQ ID NO: 1 for a composition comprising said antibody and a carrier such as PBS as taught by Harlow *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody fragment because Harlow *et al* teach that the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular). Verwoert *et al* teach that antibody to VTGASRGIGRGIA is useful for immunodetection (See page 2853, column 1, in particular).

Issue 6 -Whether Claims 11, 31-32, 34, 36-43 and 58 meet the enablement requirement of 35 USC §112`first paragraph.

The specification on page 7 line 7 defines the term "immunogenic fragment" is any fragment of HSCD which are preferably about 5 to about 15 amino acids in length which retain some biological activity or immunological activity of HSCD. The specification on page 8 defines the term "epitope" is a fragment of a molecule that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinant (epitope) given regions or three dimensional structures on the protein. The epitope may compete with intact antigen for binding to an antibody. The Office takes the position that any fragment can be used to generate antibody. However, the polypeptide "comprising" the immunogenic fragment of SEQ ID NO: 1 wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO: 1 is not the same fragment as the epitope or the fragment that makes contact with a particular antibody since the epitope may or may not compete with intact antigen or polypeptide having extra undisclosed amino acids at either or both end of the immunogenic fragment due to protein folding.

At page 10-11 of the Brief, Appellants argue that the specification discloses methods to make antibodies which specifically bind to a polypeptide having any particular amino acid sequence (page 28, line 6 to page 29, line 23, and page 51, lines 4-19). Given the information provided by SEQ ID NO: 1, one of skill in the art would be able to routinely obtain antibodies which specifically bind to any of the recited polypeptides, variants, and fragments of SEQ ID NO: 1, including any antibody which specifically binds to any epitope as set forth in claim 11.

Appellants' arguments have been fully considered but are not found to be persuasive. In response to Appellants' argument that the specification discloses methods to make antibodies which specifically bind to a polypeptide having any particular amino acid sequence, the specification discloses only two polypeptides referred to as human short-chain dehydrogenase (HSCD), as shown in Figures 1A-1D comprising SEQ ID NO: 1 (HSCD) and a short-chain acyl-CoA dehydrogenase comprising SEQ ID NO: 3. The specification also discloses antibody that specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 and SEQ ID NO: 3, a composition comprising said antibody or a labeled antibody that binds to said polypeptide comprising the amino acid sequence of SEQ ID NO: 1 for diagnostic and detection assays. The specification on page 14 discloses a "variant" of human short chain dehydrogenase (HSCD) is any amino acid sequence that is altered by one or more amino acids such as substitution, insertion and deletion including non conservative changes (See page 14 of specification, second full paragraph).

Other than the antibody that binds specifically to the specific polypeptide of SEQ ID NO: 1 or 3, the specification does not teach how to make, much less how to use any antibody that binds to any undisclosed epitope of any polypeptide at least 90% identical to the amino acid sequence of SEQ ID NO: 1 which include numerous changes and variation such as substitution, insertion and deletion. The specification does not provide guidance as to which one or more amino acids of SEQ ID NO: 1 is altered such as substitution, insertion and deletion and whether the resulting polypeptide variant retains its three dimensional structure and has biological function, much less about whether it retains antibody binding to said polypeptide variant.

A polypeptide having only 90% identity to SEQ ID NO: 1 means 10% difference in SEQ ID NO: 1, which is equivalent to having at least 31 amino acids difference (SEQ ID NO 1 which has 313 amino acids and multiply that by 10%). The specification does not provide guidance as to which one or more amino acids of SEQ ID NO: 1 is altered such as substitution, insertion and deletion and whether the resulting polypeptide variant maintains the 3D structure and retains

antibody binding. Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Further, the specification does not provide sufficient guidance and working example as to the binding specificity of any undisclosed antibody that would bind to any epitope of a polypeptide that has at least 10% difference (31 amino acids) to SEQ ID NO: 1. Abaza *et al*, of record, teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity (binding) of a protein with monoclonal antibody against the site (See abstract, in particular). Kuby *et al,* of record, teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues (fragment) or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide, let alone a polypeptide having at least 10% (31 amino acids) difference to SEQ ID NO: 1. In the absence of guidance as to the specific amino acid residues (the epitope) to which the claimed antibody binds or makes contact (the binding specificity), the claimed antibody could bind to the non disclosed amino acids (the 10%) of a variant of SEQ ID NO: 1, that is still 90% identical to SEQ ID NO: 1. In the absence of guidance as to the specific amino acid residues of a polypeptide that is at least 90% identity to SEQ ID NO 1, one of skilled in the art cannot make, much less how to use the antibody with undisclosed specificity. In fact, Applicants state on record on page 12 and repeated on page 14 second full paragraph that antibodies which specifically to a polypeptide can be made as long as that polypeptide or fragments thereof, are available. However, the amino acid sequence of a polypeptide that is 90% identical to SEQ ID NO: 1 to which the claimed antibody binds is not available.

In view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary.

At paragraph bridging page 11 and 12 of the Brief, Appellants argue that the specification has disclosed numerous examples of polypeptides "comprising" the recited polypeptides , variants, and fragments of SEQ ID NO: 1 such as fusion protein, and coupled proteins (page 7, lines 24-29, page 19, lines 26-28, page 26, lines 2-15; page 28, lines 25-27 and page 51, lines 13-19). One of skill in the art would understand how to make and use antibodies which specifically bind to the disclosed polypeptides comprising the recited polypeptides, variants and fragments of SEQ ID NO: 1 without having an explicit disclosure of every possible element which could be part of but is not essential to the claimed subject matter.

Appellants' arguments have been fully considered but are not found to be persuasive. The specification discloses only two polypeptides referred to as human short-chain dehydrogenase (HSCD), as shown in Figures 1A-1D comprising SEQ ID NO: 1 (HSCD) and a short-chain acyl-CoA dehydrogenase comprising SEQ ID NO: 3. The specification also discloses antibody that specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 and SEQ ID NO: 3, a composition comprising said antibody or a labeled antibody that binds to said polypeptide comprising the amino acid sequence of SEQ ID NO: 1 for diagnostic and detection assays. The claims encompass antibody which binds to *any* polypeptide "comprising" *any* immunogenic fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO: 1, wherein said fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO: 1 and wherein the antibody specifically binds to any epitope of the fragment. The term "comprising" is open-ended. It expands the immunogenic fragment to include additional amino acids at either or both ends in addition to SEQ ID NO: 1 or a fragment of SEQ ID NO: 1 that is at least 15 amino acids in length. There is insufficient guidance as to the binding specificity (the specific amino acid sequence of epitope to which) the claimed antibody binds or makes contact. One of skill in the art would understand how to make and use antibodies which specifically bind to the disclosed polypeptides comprising SEQ ID NO: 1. However, one of skill in the art could not predict which undisclosed antibody would bind specifically to any undisclosed polypeptide such as fusion protein that comprises additional undisclosed amino acid residues in addition to SEQ ID NO: 1 and whether antibody still binds to said undisclosed protein in the absence of guidance as to the binding specificity of the claimed antibody.

At page 12 of the Brief, Appellants argue that the claims recite antibodies which specifically bind to epitopes on the cited polypeptides, variants, and fragments of SEQ ID NO: 1.

Since the claimed antibodies specifically bind to "an epitope of a polypeptide of SEQ ID NO: 1", "an epitope of a polypeptide at least 90% identical to SEQ ID NO: 1", and "an epitope of the fragment of SEQ ID NO: 1", one skilled artisan would know how to make and use antibodies which specifically bind to epitopes of the recited polypeptides, variants, and fragment of SEQ ID NO: 1. Therefore it is irrelevant whether specification is enables antibodies which specifically bind to additional amino acid residues at either or both ends of the recited polypeptides, variants, and fragments of SEQ ID NO: 1.

Appellants' arguments have been fully considered but are not found to be persuasive. The claims encompass any antibody that bind to any epitope of SEQ ID NO: 1, any epitope of any undisclosed polypeptide that is at lest 90% identical to SEQ ID NO: 1 and any epitope of any immunogenic fragment wherein the fragment comprises at least any 15 amino acids contiguous amino acid residues of SEQ ID NO: 1. The specification discloses only two polypeptides referred to as human short-chain dehydrogenase (HSCD), as shown in Figures 1A-1D comprising SEQ ID NO: 1 (HSCD) and a short-chain acyl-CoA dehydrogenase comprising SEQ ID NO: 3. The specification also discloses antibody that specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 and SEQ ID NO: 3, a composition comprising said antibody or a labeled antibody that binds to said polypeptide comprising the amino acid sequence of SEQ ID NO: 1 for diagnostic and detection assays. The specification on page 14 discloses a "variant" of human short chain dehydrogenase (HSCD) is any amino acid sequence that is altered by one or more amino acids such as substitution, insertion and deletion including non conservative changes (See page 14 of specification, second full paragraph).

Other than the antibody that binds specifically to SEQ ID NO: 1 or 3, there is insufficient guidance as to the binding specificity of the claimed antibody such as the amino acid sequence of the epitope (the specific amino acid residues) to which the claimed antibody binds. As to antibody that binds to epitope of a polypeptide at least 90% identical to SEQ ID NO: 1, the claimed antibody could very well bind to the epitope where there is at least 10% difference to SEQ ID NO: 1. There is insufficient guidance as to the structure, much less about the function of the any polypeptide at least 90% identical to SEQ ID NO: 1. There is no working examples demonstrating that the claimed antibody could bind to any undisclosed polypeptide such as polypeptide at least 90% identical to SEQ ID NO: 1 or any epitope of any immunogenic fragment comprises at least 15 contiguous amino acid residues to SEQ ID NO: 1. Given the indefinite number of undisclosed polypeptide such as variant of SEQ ID NO: 1, it is unpredictable which

undisclosed polypeptide would be useful for generating antibody that binds specifically to any epitope of a polypeptide at least 90% identical to SEQ ID NO: 1. Those cited references establish that a single amino acid change in the antigen render the antigen unrecognizable by the antibody. Because of the unpredictability and lack of guidance, an undue experimentation would be required to determine which modifications would be acceptable to retain structural and functional activity of the claimed variant polypeptide and fragments of SEQ ID NO: 1. Therefore, one of ordinary skill in the art would not be able to determine, without undue experimentation, the positions in the SEQ ID NO:1 polypeptide which are tolerant to change and the nature and extent of changes that can be made in these positions and the claimed antibody still binds.

With regard to antibody specifically binds to any epitope of any undisclosed immunogenic fragment comprises additional undisclosed amino acids, there is insufficient guidance as to the structure of the polypeptide as set forth in claim 11c because of the additional undisclosed amino acid at either or both ends of the immunogenic fragment and whether the antibody generated from any undisclosed fragment having extra undisclosed amino acids would bind specifically to any epitope of the fragment of SEQ ID NO: 1. The Kuby et al reference establishes that **antibody specificity** generated from a fragment differs from antibody specificity directed against the native full-length polypeptide, let alone any fusion protein. Because of the unpredictability and lack of guidance, an undue experimentation would be required to determine which undisclosed polypeptide comprising an immunogenic fragment at least 15 contiguous amino acids residues of SEQ ID NO: 1 would generate antibody that specifically binds to any epitope of any undisclosed fragment of SEQ ID NO: 1.

At paragraph bridging page 14 and 15 of the Brief, Appellants argue that Ngo et al teachings regarding the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. it activity) are not well understood and are not predictable, it is not necessary to predict protein structure in order to predict protein function, since it is possible to know a great deal about a protein's biological function without knowing its three-dimensional structure. Appellants argue that the functions of many proteins can be predicted based upon homology to proteins with known functions, even when no three-dimensional structure of any protein in the family is known. Appellants conclude that Ngo et al teachings are not relevant. Appellants argue that natural selection tends to conserve those residues critical for protein structure and function during the course of evolution.

Appellants' arguments have been fully considered but are not found to be persuasive. Appellants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Therefore, one of ordinary skill in the art would not be able to determine, without undue experimentation, the positions in the SEQ ID NO:1 polypeptide which are tolerant to change and the nature and extent of changes that can be made in these positions and the claimed antibody still binds. Therefore, it would require an undue amount of experimentation for one of skill in the art to arrive at immunogenic fragments or a naturally occurring amino acid sequence at 90% identical to an amino acid sequence of SEQ ID NO: 1.

At page 15 of the Brief, Appellants argue that the Abaza reference has no bearing on whether one of skill in the art could make and/or use the claimed antibodies without undue experimentation. Even if a polypeptide variant has an amino acid substitution which drastically affects the reactivity of a monoclonal antibody which specifically binds to the parent polypeptide, a skilled artisan would still know how to use that polypeptide variant to make antibodies which specifically bind to the polypeptide variant.

This is not found to be persuasive. The Abaza reference establishes that a single amino acid change in the antigen renders the antigen unrecognizable by the antibody. The specification fails to provide insufficient guidance as to the structure, much less about the function of the any polypeptide at least 90% identical to SEQ ID NO: 1. Further, there is no working examples demonstrating that the claimed antibody could bind to any undisclosed polypeptide such as any epitope of any polypeptide at least 90% identical to SEQ ID NO: 1 or any epitope of any polypeptide "comprising" any immunogenic fragment wherein the fragment comprises at least 15 contiguous amino acid residues to SEQ ID NO: 1. Given the indefinite number of undisclosed variants of SEQ ID NO: 1, it is unpredictable which undisclosed polypeptide would be useful for generating antibody that binds specifically to any epitope of a polypeptide at least 90% identical to SEQ ID NO: 1. In the absence of guidance as to the specific amino acid residues (the epitope)

to which the claimed antibody binds or makes contact (the binding specificity), the claimed antibody could bind to the non disclosed amino acids (the 10%) of a variant of SEQ ID NO: 1, that is still 90% identical to SEQ ID NO: 1. Because of the unpredictability and lack of guidance, an undue experimentation would be required to determine which modifications would be acceptable to retain occluding structural and functional activity of the claimed variant polypeptide and fragments of SEQ ID NO: 1. Therefore, one of ordinary skill in the art would not be able to determine, without undue experimentation, the positions in the SEQ ID NO: 1 polypeptide which are tolerant to change and the nature and extent of changes that can be made in these positions and the claimed antibody still binds.

At paragraph bridging page 15 and 16, Appellants argue that there is no statutory requirement that an invention actually be reduced to practice in order to for that invention to be patentable. Methods of making and using antibodies which specifically bind to polypeptides including polypeptides based on the SEQ ID NO: 1 have been disclosed (page 28, line 6, to page 29, line 23, and page 51, line 4 to page 52, line 2).

Appellants' arguments have been fully considered but are not found to be persuasive. Although the method of making antibodies to the specific polypeptide comprising SEQ ID NO: 1 has been disclosed, the specification does not appear to have provided sufficient guidance as to which epitope (amino acid residues) the claimed antibodies bind to which undisclosed polypeptide at least 90% identical to SEQ ID NO: 1 or which undisclosed polypeptide "comprising" any immunogenic fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO: 1. The specification does not provide any working examples of any variants and fragments of SEQ ID NO: 1, in turn, could be used for making antibody that binds specifically to said variants and fragments of SEQ ID NO: 1. Thus it would require undue experimentation of the skilled artisan to determine which variants and fragments of SEQ ID NO: 1 would have the biologically function as the full length polypeptide. Moreover, the number of changes encompassed by "at least about 90% identity" are numerous that it would still require undo experimentation of the skilled artisan to make these changes and then identify which polypeptides, if any, had the desired activities. Until the time when such variants and fragments of SEQ ID NO: 1 are identified, then one skill in the art can make antibodies against those variants and fragments of SEQ ID NO: 1.

At page 16 of the Brief, Appellants argue that the claimed chimeric antibodies are fully enabled and no guidance "for in vivo therapeutic use" is necessary since the methods to treat patients with the recited chimeric antibodies are not recited in the claims. The recited chimeric antibody could be used, for example, to detect and/or purifying antibody.

Appellants' arguments have been fully considered but are not found to be persuasive. The intended use for the composition comprising the claimed antibody such as monoclonal, chimeric, single chain, Fab fragment, (Fab')2 fragment and humanized antibody and an acceptable excipient as discloses on page 32, line 14 of the specification is for in vivo therapy.

At paragraph bridging page 16 and 17 of the Brief, Appellants argue that the Examiner has failed to provide any reasons why one would doubt that the guidance provided by the present specification would enable one to make an use the claimed antibodies which specifically bind to the recited polypeptides, variants and fragments of SEQ ID NO: 1.

Appellants' arguments have been fully considered but are not found to be persuasive. Appellant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Therefore, it would require an undue amount of experimentation for one of skill in the art to arrive at immunogenic fragments or a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1. Given that the immunogenic fragments or a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1 are not enable, it follows that the method of making antibodies using said variants and fragment comprising SEQ ID NO: 1 are not enabled. It also follows that antibody that binds to any epitope of any undisclosed polypeptide that is at least 90% identical to SEQ ID NO: 1 is not enabled.

Issue 7 - Whether Claims 11, 31-32, 34, 36-43 and 58 meet the written description requirement of 35 USC §112`first paragraph.

At page 19-20 of the Brief, Appellants argue that the specification discloses a polypeptide of SEQ ID NO: 1. Variants of SEQ IDNO: 1 are described in the specification at page 3, lines 5-6, page 6, line 18 to page 7, page 7, lines 9-12, page 14, line 12-19 and page 15, lines 15-18 and fragments of SEQ IDNO: 1 are described at page 3, lines 2-4, page 7, lines 5-9, page 8, lines 15-18, lines 21-25, and page 51, lines 7-16, page 50. One of ordinary skill in the would recognize polypeptide sequences which are variants that are at least 90% identical to SEQ ID NO: 1 and polypeptide which are fragments of SEQ ID NO: 1.

Appellants' arguments have been fully considered but are not found to be persuasive. Specifically, appellants have not teach any naturally occurring variant that is at least 90% identical to SEQ ID NO: 1 neither did appellant teach any fragments of SEQ ID NO: 1, see sequence listing in particular, much less about the binding specificity of claimed antibody or epitope of any polypeptide at least 90% identical to SEQ ID NO: 1 or polypeptide comprising immunogenic fragment of SEQ ID NO: 1 to which the claimed antibody binds. Further, the Examiner notes that the claimed invention, which is drawn to a genus, is not adequately described in the specification since there is a lack of representative number of species as disclosed.

The specification discloses only antibody that specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, a composition comprising said antibody for diagnostic and detection assays. The specification on page 14 discloses a "variant" of human short chain dehydrogenase (HSCD) is any amino acid sequence that is altered by one or more amino acids such as substitution, insertion and deletion (See page 14 of specification, second full paragraph).

With the exception of the specific antibody that binds to the specific polypeptide of SEQ ID NO: 1 mentioned above, there is insufficient written description about the structure of *any* immunogenic fragment "comprises" at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO: 1 because the term "comprising" is open-ended. It expands the fragment to include additional amino acids at either or both ends. There is inadequate written description about the undisclosed amino acids at either or both ends of the fragment, much less about the epitope to which the antibody binds in said undisclosed fragment.

Further, there is insufficient written description about the structure such as the specific amino acid sequence of any polypeptide that is at least 90% identical to SEQ ID NO: 1 to which

the antibody binds. A 90% identity to SEQ ID NO: 1 means 10% difference, which is equivalent to having 31 amino acids difference (SEQ ID NO 1 which has 313 amino acids and multiply that by 10%). In the absence of guidance as to the specific amino acid residues (the epitope) to which the claimed antibody binds or makes contact (the binding specificity), the claimed antibody could bind to the non disclosed amino acids (the 10%) of a variant of SEQ ID NO: 1, that is still 90% identical to SEQ ID NO: 1. Given the indefinite number of undisclosed polypeptide that is at least 90% identical to SEQ ID NO: 1, the variants of SEQ ID NO: 1 is not adequately described. Since the variants of SEQ ID NO: 1 is not adequately described, it follows that the claimed antibody that binds to any variants of SEQ ID NO: 1 such as any polypeptide that is at least 90% identical to SEQ ID NO: 1 is not adequately described.

Finally, given the lack of a written description of any additional variants of SEQ ID NO: 1 or immunogenic fragment of SEQ ID NO: 1 to which the claimed antibody that binds, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of antibody to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

At page 21-23 of the Brief, Appellants argue that the present claims specifically define the claimed genus through the recitation of chemical structure. The claimed antibodies which specifically bind the recited variants and fragments of SEQ ID NO: 1 polypeptide have been described by chemical structure (e.g. relation of the recited polypeptide variants and fragments of SEQ ID NO: 1), physical properties (e.g. occurrence in nature of the recited polypeptide variants) and chemical properties (e.g., possession of CoA dehydrogenase activity). Appellants summarize case laws and assert that the claims in the instant application define the variants of SEQ ID NO: 1 in terms of chemical structure rather than in terms of functional characteristics. Appellants contend that if such functional recitations were included in the claims, it would add to the structural characterization of the recited polypeptides. Appellants argue that by failing to base its written description inquiry "on whatever is now claimed", the Final Office Action failed to provide an adequate analysis of the present claims and how they differ from those found not to

satisfy the written description requirement in Fiers v. Revel,25 USPQ2d 1601, 1606 (Fed. Cir. 1993).

Appellants' argument have been fully considered but are not found to be persuasive because Appellants have not provided evidence to demonstrate that the skilled artisan would be able to envision the detailed structure of the infinite number of polypeptides to which the antibody binds as recited in the claims. The description of antibody that binds to a polypeptide of SEQ ID NO: 1 in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polypeptides which incorporate all mutants, derivatives, variants and fragments having at least 90% identity to the amino acid sequences of SEQ ID NO: 1 to which the antibody binds. Therefore, only antibody that binds specifically to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

On paragraph bridging page 23 and 24 of the Brief, Appellants assert that the claims at issue do not describe a genus which is highly variant, but rather a genus that is narrow in scope. Appellant states that the variant language of the present claims recites, for example, polypeptides comprising "a naturally-occurring human amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 1 (SEQ ID NO: 1 has 313 amino acids). Appellants argue that this variation is far less than that of all potential short-chain dehydrogenase related to SEQ ID NO: 1.

Appellants' arguments have been considered but are not found to be persuasive. As discussed above, Appellants have not provided evidence to demonstrate that the skilled artisan would be able to envision the detailed structure of the infinite number of polypeptides to which the claimed antibody binds as recited in the claims. The specification and claims do not indicate what characteristics are shared by members of the genus. The scope of the claims includes numerous structural variants and the genus is highly variant because a significant number of structural differences between genus members are permitted. However, the specification and claims do not provide any guidance as to what changes should be made and what structural features that distinguish polypeptides in the same genus from others in the protein class are absent from the specification. The specification fails to disclose the common characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 1 is insufficient to

describe the genus. Since the variants of SEQ ID NO: 1 is not adequately described, it follows that the claimed antibody that binds to any variants of SEQ ID NO: 1 such as any polypeptide that is at least 90% identical to SEQ ID NO: 1 is not adequately described.

At the bottom of page 24 through page 25 of the Brief, Appellants contend that much has happened in the development of recombinant DNA technology in the 16 or more years from the time of filing of the applications involved in Lilly and Fiers and the present application. Appellants indicate that, for example, PCR, highly efficient cloning and DNA sequencing technology has been developed. Appellants assert that with the remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO: 1, the additional extensive detail provided by the application, the present inventors were in possession of the antibody that binds to variants and fragments of SEQ ID NO: 1 as recited by the claims at the time of filing of this application.

Appellants' arguments have been considered but are not found to be persuasive because the broad brush discussion of making and screening for allelic variants does not constitute a disclosure of a representative number of members. No such variants of SEQ ID NO: 1 that is 90% identical to SEQ ID NO: 1 were made or shown to have activity and retains antibody binding. Only the polypeptide of SEQ ID NO: 1 and SEQ ID NO: 3 are disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants. Given the indefinite number of undisclosed polypeptide that is at least 90% identical to SEQ ID NO: 1, the variants of SEQ ID NO: 1 is not adequately described. Since the variants of SEQ ID NO: 1 is not adequately described, it follows that the claimed antibody that binds to any variants of SEQ ID NO: 1 such as any polypeptide that is at least 90% identical to SEQ ID NO: 1 is not adequately described.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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